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09/821,832	03/30/2001	Thomas Tuschl	0399.2008-002	6240

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EXAMINER	
WOLLENBERGER, LOUIS V	
ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/821,832	TUSCHL ET AL.	
	Examiner	Art Unit	
	Louis V. Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *76-78,81,86-88,91,106,108,110,112 and 115-123* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *76-78,81,86-88,91,106,108,110,112 and 115-123* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/10/02*. *10/09/07*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response, filed 8/2/2007, to the Non-Final Office Action mailed 1/29/2007 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 1/29/2007 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed 8/2/2007, claims 76–78, 81, 86–88, 91, 106, 108, 110, 112, and 115–123 are pending and under examination.

Information Disclosure Statement

Upon review of the prosecution record it is unclear whether the IDS filed 6/10/2002 had been considered by the previous Examiner. For clarity, then, the initialed and signed IDS filed 6/10/2002 is enclosed herewith, indicating that all references disclosed therein have been considered by the instant Examiner.

Double Patenting

The list of potentially conflicting applications in this case is extensive

Additional applications and issued patents, not relied on in the rejections below, which may claim the same or similar subject matter include: 10/832,248; 10/638,253; 10/832,432; 11/880,355; and 11/880,464.

If Applicants are aware of any commonly owned pending applications or issued patents, which are not listed below and which claim conflicting subject matter, it is Applicants' duty to disclose these applications or patents, and to submit an appropriate terminal disclaimer over these applications or patents as pertinent to the instant invention.

Claims 76–78, 81, 86–88, 91, 106, 108, 110, 112, and 115–123 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 17, 20-23, 76, and 80 of copending Application No. 10/255,568, as presented on 10/5/2007. Although the conflicting claims are not identical, they are not patentably distinct from each other because the conflicting application claims a method of mediating RNA interference of an mRNA in a cell comprising introducing into the cell double stranded RNA of from about 21 to about 23 nucleotides in length, and embodiments thereof wherein the mRNA is mammalian cellular mRNA.

Therefore, one of ordinary skill in the art would conclude that the invention defined in the claims at issue is anticipated by, or would have been an obvious variation of, the invention defined in a claim in the conflicting application.

In the previous Action, mailed 1/29/07, it was pointed out by the Examiner that:

1) MPEP §804, Section I, Part B.1 states in part that "If "provisional" ODP rejections in two applications are the only rejections remaining in those

applications, the examiner should withdraw the ODP rejection in the earlier filed application thereby permitting that application to issue without need of a terminal disclaimer. A terminal disclaimer must be required in the later-filed application before the ODP rejection can be withdrawn and the application permitted to issue";

2) the conflicting applications are effectively filed on the same day. Thus, Application 10/255,568 is not a "later-filed" application;

3) a terminal disclaimer has not been required or voluntarily filed in conflicting application 10/255,568

4) the instant ODP rejection is not the only rejection remaining in the instant application; and that

5) the conflicting applications are not divisional applications of one another. The applications were not filed as the result of a restriction requirement in one or the other. The applications were voluntarily filed as separate applications. Thus, the prohibition against using the '568 Application as a reference against the instant application does not apply.

Therefore, the instant rejection is maintained because the products claimed by the instant application are obvious in view of the methods now claimed in copending Application No. 10/255,568.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Applicant's arguments presented 8/2/07

Applicant argues the instant rejection is inconsistent with the Office's reasons for restricting applicant to method or product claims in any single application.

In response, the Examiner respectfully points out that in the instant application, where the examiner has required restriction between product and process claims, and where applicant has elected claims directed to the product, should the product claims subsequently be found allowable, applicant retains the right to reinstate cancelled process claims that depend from or otherwise require all the limitations of the allowable product claim. In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. See MPEP § 821.04(b). Rejoined methods claims would be patentably indistinct from those in the '568 case.

Furthermore, the Restriction Requirement by the Office was directed to claims filed in a single application and made no formal judgments as to the distinction between claims filed in separate, non-related, copending cases.

Applicant has been given ample opportunity to take advantage of the provisions of 35 USC §121 to file divisional applications claiming methods or products, as the case may be, to obviate rejections under the judicially created doctrine of obviousness-type double patenting. Applicant's enjoy no such protection in cases that are voluntarily filed, copending, non-related, and separately prosecuted.

***

Claims 76–78, 81, 86–88, 91, 106, 108, 110, 112, and 115–123 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 34-55 of copending Application No. 11/142,866. Although the conflicting claims are not identical, they are not patentably distinct from each other because the conflicting application claims a method for chemically and enzymatically synthesizing nuclease resistant (i.e., stabilized) siRNAs of 19-25 nucleotides that mediate RNA interference.

Absent convincing evidence to the contrary, the methods claimed therein would result in the production of dsRNAs having 3' hydroxyls.

Response to Arguments

Applicant argues the pending claims are directed to methods of chemically synthesizing interfering RNAs having recited structural features. By contrast, the claims of the instant case are directed to a broad genus of interfering RNAs that can be produced by a variety of materially distinct processes. For this reason, Applicants respectfully submit that the provisional double patenting rejection in the instant case is substantively without merit and request withdrawal of the rejection.

Applicant's arguments have been fully considered but are not persuasive.

One of skill would recognize that the methods for making dsRNA claimed in '866 could be used to make the dsRNAs now claimed in the instant application. Therefore, one of ordinary skill in the art would conclude that the products defined in the claims at issue are anticipated by, or would have been obvious in view of the methods for making defined in the claims in the conflicting application.

MPEP §804, Section I, Part B.1 states in part that "If "provisional" ODP rejections in two applications are the only rejections remaining in those applications, the examiner should withdraw the ODP rejection in the earlier filed application thereby permitting that application to issue without need of a terminal disclaimer. A terminal disclaimer must be required in the later-filed application before the ODP rejection can be withdrawn and the application permitted to issue."

Application No. 11/142,866 is a later filed application. However, a terminal disclaimer has not been required or voluntarily filed in conflicting application Application No. 11/142,866. Additionally, the instant ODP rejection is not the only rejection remaining in the instant application.

Therefore, the instant rejection is maintained.

***

Claims 76–78, 81, 86–88, 91, 106, 108, 110, 112, and 115–123 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 48, 49, 51, 53-57, 60-64, 67-73, and 75-125 of copending Application No. 10/433,050. Although the conflicting claims are not identical, they are not patentably distinct from each other because Application 10/433050 claims an isolated double stranded RNA molecule 19-23 nucleotides in length that mediates target-specific modifications of a mammalian gene.

Therefore, one of ordinary skill in the art would conclude that the invention defined in the claims at issue is anticipated by, or would have been an obvious variation of, the invention defined in a claim in the conflicting application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Objections—withdrawn

The objection to Claim 106 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is withdrawn in view of Applicant's amendment to the claim.

Claim Rejections - 35 USC § 112—withdrawn

The rejection of Claims 76–78, 81, 86–88, 91, 106, 108, 110, 112, and 115–123 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of Applicant's amendments to the claims and in view of Applicant's arguments, which are found persuasive.

In view of the amendment to claim 106 (above) and in view of Applicant's arguments stating that isolated RNA molecules having sequences with less than perfect sequence correspondence are within the scope of the invention (Remarks, page 10), for purposes of this examination, imperfectly matched sequences—sequences lacking less than 100% complementarity with the target mammalian mRNA—are within the scope of the instant claims so long as the sequences have sufficient sequence correspondence to an mRNA to mediate its cleavage by RNAi.

***

The rejection of Claims 86, 88, 106, 108, 112, and 115–123 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject

matter which applicant regards as the invention because the limitation "wherein cleavage is directed within the region of sequence correspondence" lacks clear antecedent basis in the claims is withdrawn in view of Applicant's amendments to the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 76–78, 81, 86–88, 91, 108, and 117 are rejected under 35 U.S.C. 102(b) as being anticipated by Manche et al. (1992) *Molecular and Cellular Biology* 12:5238–5248, as evidenced by Stratagene pBluescript II Phagemid Vectors Instruction Manual for Catalog # 212207, downloaded from the Stratagene, Inc. website on January 11, 2007 (copy enclosed), and a Basic Local Alignment Search Tool (BLAST) analysis, available through NCBI, of nucleic acid sequence "cccggtacccagcttttgttccc" completed on January 11, 2007 (results enclosed).

Representative, independent claim 76 recites an isolated double-stranded RNA of from 21 to 23 nucleotides, in the form of two separate RNA strands which are not covalentlv linked, that has sequence correspondence to an mRNA and mediates RNA interference by directing cleavage of the mRNA to which it corresponds, wherein cleavage is directed within the region of sequence correspondence with the isolated RNA, and wherein the mRNA is mammalian cellular mRNA.

Manche et al. teach the production and isolation of a series of short, double stranded RNAs for use in a study of the interaction and activation of the interferon-induced protein kinase DAI. With regard to the instant claims, Manche et al. teach a 23-nucleotide double stranded RNA at page 5239 (see the *Hae* III fragment in Fig. 1; see also Materials and Methods, pp. 5239-40; and Characteristics of synthetic dsRNA, pp. 5240-1).

For example, at page 5240, Manche et al. state that "Duplexed RNAs of defined sizes were made by annealing a 358-nt transcript synthesized by T7 RNA polymerase with complementary transcripts of various lengths synthesized by T3 RNA polymerase (Fig. 1A). After digestion of the RNA tails and residual single-stranded RNA, the dsRNAs were purified by electrophoresis in nondenaturing polyacrylamide gels. When analyzed in denaturing conditions (Fig. 1B), the individual strands of the dsRNA molecules were slightly heterogeneous, with chain lengths a few nucleotides longer or shorter than the input single strands as a result of the trimming process. When examined in a nondenaturing gel, however,the dsRNAs migrated as discrete bands, with mobilities similar to those of dsDNA markers (see Fig. 5A, lanes 3 to 9). As expected, the duplexes were sensitive to digestion with RNase III, a dsRNA-specific enzyme, but resistant to digestion by single-stranded specific nucleases except after denaturation (data not shown)."

Accordingly, the short dsRNAs are taught as being isolated and used systematically, in a substantially purified form to study their effect, if any, in a DAI kinase activation assay. Manche et al. teach that 23-mers only slightly activate DAI, whereas full activity was approached with 55- to 85-bp dsRNAs (page 5240 and Fig. 2, page 5241).

While Manche et al. do not specifically teach the sequence of the isolated short dsRNAs, nor provide any suggestion that the isolated short dsRNAs will or will not inhibit the expression of a mammalian gene, Manche et al. teach that the the plasmid pBSII KS+, from Stratagene, Inc.,

La Jolla, Calif. was used as the source of the short dsRNAs. More specifically, the dsRNAs were produced by restriction endonuclease digestion of the multiple cloning site region to produce templates for in vitro transcription. The transcribed products were then purified and annealed, and then digested with RNase to produce the dsRNAs used in the study (see materials and methods, pp. 5239-5240, and Fig. 1B).

The pBSII KS+ vector appears to correspond to the pBluescript II KS (+), described on page 4 of the Stratagene pBluescript II Phagemid Vectors Instruction Manual, available online from the Stratagene website (copy enclosed). Based on the multiple cloning site map, provided at page 4 of the Manual, it appears that the *Hae* III fragment of the vector consists of the sequence "cccggtacccagcttttgttccc." *Hae* III appears to cut just 5' of the *Kpn* I site at the "ggcc" palindrome.

A BLAST analysis of this sequence against the refseq_rna database shows that the sequence shares substantial "correspondence to" a number of rat, mouse, and human mRNAs, including Homo sapiens methyltransferase 11 domain containing 1 (METT11D1), transcript variant 2, mRNA (see, for example, page 7 of 12 of the BLAST search results, enclosed).

Accordingly, while Manche et al. is silent as to the RNA interference properties, if any, of the disclosed 23-nucleotide double stranded RNA, Manche et al. is considered to inherently disclose a 23-nucleotide dsRNA that "has sequence correspondence" and complementarity to a mammalian cellular mRNA, as required by the instant claims. Given that sequence correspondence and/or complementarity is an essential feature of interfering dsRNAs insofar as their ability to sequence-specifically inhibit gene expression and act as a guide for the RISC, it

would appear that Manche et al. teach a dsRNA product that meets each of the structural limitations of the instant claims.

Though silent as to an inherent property, Manche et al. need not teach or recognize this inherent feature to anticipate the instant claims, since, as set forth in MPEP §2112, "There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure *at the time of invention*, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003)."

And although the Manche et al. 23-mer does not appear to share 100% identity and/or sequence complementarity with a mammalian mRNA, a substantial portion of the 23-mer does match or is complementary to several mammalian mRNAs (see pages 3 and 4, for example). This finding, along with the teaching in the specification at page 3, lines 15-20, that, with regard to siRNAs used in the invention, "It is not necessary that there be perfect correspondence of the sequences, but the correspondence must be sufficient to enable the RNA to direct RNAi cleavage of the target mRNA" is considered to be sufficient to indicate that there is a basis in fact to support the determination that the dsRNA disclosed by Manche et al. is inherently RNAi competent against at least one mammalian mRNA as shown in the accompanying BLAST analysis (MPEP §2112, Section IV).

Accordingly, because the 23-nucleotide double stranded RNA disclosed by Manche et al. meets each the structural requirements of the instant claims, it would necessarily possess the biochemical properties recited in the claims. A compound and its properties are inseparable.

Therefore, Manche et al. anticipates the instant claims.

As a practical matter, the Patent Office is not equipped to manufacture products by the myriad of processes put before it and then obtain prior art products and make physical comparisons therewith." *In re Brown*, 459 F.2d 531, 535, 173 USPQ 685, 688 (CCPA 1972) (MPEP §2113).

In the instant case, the Office is not equipped with a laboratory to manufacture and verify the RNAi competency of perfectly or imperfectly matched sequences found in the prior art.

MPEP §2112 Requirements of Rejection Based on Inherency; Burden of Proof
A REJECTION UNDER 35 U.S.C. 102/103 CAN BE MADE WHEN THE PRIOR ART PRODUCT SEEMS TO BE IDENTICAL EXCEPT THAT THE PRIOR ART IS SILENT AS TO AN INHERENT CHARACTERISTIC

> Where applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection. "There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102." *In re Best*, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977). This same rationale should also apply to product, apparatus, and process claims claimed in terms of function, property or characteristic. Therefore, a 35 U.S.C. 102/103 rejection is appropriate for these types of claims as well as for composition claims.

A REFERENCE TEACHING PRODUCT APPEARING TO BE SUBSTANTIALLY IDENTICAL IS MADE THE BASIS OF A REJECTION, AND THE EXAMINER PRESENTS EVIDENCE OR REASONING TENDING TO SHOW INHERENCY, THE BURDEN SHIFTS TO THE APPLICANT TO SHOW AN UNOBVIOUS DIFFERENCE

"[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency' under 35 U.S.C. 102, on prima facie obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted]." The burden of proof is similar to that required with respect to product-by-process claims. *In re Fitzgerald,* 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting *In re Best,* 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)).

Claims 78, 86, 88, 110, and 112 are drafted in the product-by-process format. Even though the reference may not describe the production of the molecule using the methods identical to that recited in the claims, the recitation of a process limitation in the instant claims is not viewed as positively limiting the claimed product absent a showing that the process of making recited in the instant claims imparts a novel or unexpected property to the claimed

product, as it is assumed that equivalent products are obtainable by multiple routes. The burden is placed upon the applicants to establish a patentable distinction between the claimed and disclosed prior art products.

The method in which the isolated RNAs were produced is immaterial to their patentability. "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re* Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP 2113.

Response to Applicant's arguments

Applicant argues, but provides no substantiating evidence, that the Manche molecule does not mediate RNAi.

For example, Applicant states that, from a technical standpoint, for reasons having to do with the method and enzymes used by Manche et al. to create the dsRNAs disclosed therein at Fig. 1, the 23-mer of Manche et al. is actually a 23-nt/24-nt duplex, which is not embraced by the instant claims.

This argument is not persuasive because, whether or not the 23-nt dsRNA disclosed by Manche et al. was composed in full or in part of 23/24-nt duplexes, Manche et al. expressly describe and illustrate the molecule as a 23-nucleotide dsRNA. One of skill would recognize the disclosure on its face as such. Therefore, Manche et al. taught a 23-nucleotide dsRNA. Furthermore, Manche et al. recognized and communicated the possibility of strand length heterogeneity, indicating that any given preparation may not be of uniform length (page 5240). Indeed, given the nature of the study of Manche et al., which was, after all, a study of the effect of dsRNA length on the DAI response, it is clear that Manche et al. took pains to establish and control for dsRNA length.

Applicant's present no convincing evidence that the 23-mer dsRNA disclosed by Manche et al. does not contain 23/23 nt duplexes, even though Manche et al. taught that the preparation was 23 nucleotides in length. Similarly, Applicant argues but provides no evidence that the preparation of Manche et al. would fail to mediate RNAi.

Applicant further provides a lengthy technical discussion alleging that, due to the nature of T3 and T7 polymerases used by Manche et al. to create the dsRNAs, the method of Manche et al. would inherently produce dsRNAs lacking the requisite fine structure required by RNAi-competent molecules.

For example, Applicant argues the dsRNA of Manche et al. would necessarily have a 5' triphosphate on one strand and a 5' hydroxyl on the other. Applicant argues it is well-known that a single 5' phosphate (ie., a 5'-monophosphate) is required for small RNA to function in mediating RNA interference, and point to Nykhen et al., Cell, 107: 309-32 1 (2001) for support.

This argument is not persuasive because Applicant provides no evidence that the triphosphate and hydroxyl would abolish RNAi, and since the claims encompass and do not exclude these structures. Applicant's arguments and technical reasoning may be sound, but the conclusion remains speculative. High energy intermediates such as triphosphates would likely be hydrolyzed to the lower energy monophosphate prior to or following introduction into the cell. Finally, post-filing art, co-authored by one of the co-inventors, expressly taught that the 5' phosphate is not essential for siRNA function, in contrast to Applicant's statements. For example, Elabashir et al. (2002) *Methods* 26:199-213 taught that "...siRNAs with free 5'-hydroxyls and 2-nt 3' overhangs are readily phosphorylated in *D. melanogaster* embryo lysates

and also in extracts from human HeLa cells." "...[C]omparison of the mammalian RNAi efficiencies of 5'-phosphorylated and non-phosphorylated siRNAs did not reveal any sizable differences." "Thus, siRNAs synthesized or purchased without a 5'phosphate group can be used in knockdown experiments" (page 201, right column).

Additionally, Applicant argues, but provides no evidence, that the Manche molecule exceeds the normal acceptable free energy threshold of RNAi molecules due to the high G/C content at the ends of the molecule, which would prevent the molecule from effectively loading into the RISC. Applicant argues that even if the molecule were of the correct size and comprised the appropriate end structure the sequence itself is not RNAi competent.

The Examiner notes that the instant claims are not currently rejected for lack of written description. Here Applicant argues certain sequences of 21 to 23 nucleotides in length are non-operative by pointing to rules that were not available at the time of filing. These molecules are not described in the application as filed.

Furthermore, Applicant is reminded that the Manche molecule does not have to be highly active or hyperfunctional. The molecule simply needs "to mediate RNA interference" at any level. Even if the molecule only reduces the level of a target mRNA by 1%, so long as the molecule reduces mRNA by an RNAi mechanism the molecule meets the structural/functional requirements of the claims. Applicant has not shown that the Manche molecule does not mediate RNAi interference.

Therefore, Applicant's arguments are insufficient to rebut the evidence in the prior art, disclosing a dsRNA molecule within the scope of the claims.

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Claims 76-78, 81, 86-88, 91, 108, 110, 112, 116, 118, 119, 120, and 122 are rejected under 35 U.S.C. 102(b) as being anticipated by Bevilacqua et al. (1996) *Biochemistry* 35:9983-9994, as evidenced by the NCBI BLAST, as available online on 10/12/2007 at http://www.ncbi.nlm.nih.gov/blast.

Bevilacqua et al. taught 22-nucleotide dsRNAs. In one instance, the dsRNA comprises the sequence "GGGUUCCCUGGUUUCGGUCUCU" (see page 9987, Fig. 3); in another, the sequence "CUGGGUUCCCUGGUUUCGGUCU" (page 9988, Fig. 4). In addition, Bevilacqua et al. taught 22-nucleotide dsRNAs comprising one or more deoxyribonucleotides, as well as dsRNAs substituted with one or more 2'-OCH_3 groups (see Fig. 4 and page 9988, bottom left paragraph; Fig. 5, page 9989; and Fig. 6, page 9990.) See also abstract and discussion, pp. 9991-9992.

In at least one instance, GGGUUCCCUGGUUUCGGUCUCU, the dsRNA shows sequence correspondence to a human mRNA, GenBank NM_022904. See alignment below.

```
>  ref|NM_022904.1|  Homo sapiens hypothetical protein FLJ21438 (FLJ21438), mRNA
Length=3290

 Score = 28.2 bits (14),  Expect =    31
 Identities = 14/14 (100%), Gaps = 0/14 (0%)
 Strand=Plus/Minus

Query  9     CCTGGTTTCGGTCT  22
             ||||||||||||||
Sbjct  2727  CCTGGTTTCGGTCT  2714
```

In another, CUGGGUUCCCUGGUUUCGGUCU, the dsRNA shows sequence correspondence to a human mRNA, GenBank NM_002234. See alignment below.

```
>  ref|NM_002234.2|  Homo sapiens potassium voltage-gated channel, shaker-related
subfamily, member 5 (KCNA5), mRNA
Length=2865

 Score = 28.2 bits (14),  Expect =    31
```

```
 Identities = 14/14 (100%), Gaps = 0/14 (0%)
 Strand=Plus/Minus

Query  2     TGGGTTCCCTGGTT  15
             ||||||||||||||
Sbjct  1617  TGGGTTCCCTGGTT  1604
```

Therefore, Bevilacqua et al. disclose dsRNAs meeting the structural requirements of the claims. Therefore, because a compound and its properties are inseparable, the dsRNAs of Bevilacqua would possess the properties intrinsic to such compounds, including the ability to mediate RNAi.

As a practical matter, the Patent Office is not equipped to manufacture products by the myriad of processes put before it and then obtain prior art products and make physical comparisons therewith." *In re Brown*, 459 F.2d 531, 535, 173 USPQ 685, 688 (CCPA 1972) (MPEP §2113).

In the instant case, the Office is not equipped with a laboratory to manufacture and verify the RNAi competency of perfectly or imperfectly matched sequences found in the prior art.

Burden is shifted to applicant to show by way of evidence that the dsRNAs do no in fact possess the properties

MPEP §2112 Requirements of Rejection Based on Inherency; Burden of Proof
A REJECTION UNDER 35 U.S.C. 102/103 CAN BE MADE WHEN THE PRIOR ART PRODUCT SEEMS TO BE IDENTICAL EXCEPT THAT THE PRIOR ART IS SILENT AS TO AN INHERENT CHARACTERISTIC

> Where applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection. "There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102." *In re Best*, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977). This same rationale should also apply to product, apparatus, and

process claims claimed in terms of function, property or characteristic. Therefore, a 35 U.S.C. 102/103 rejection is appropriate for these types of claims as well as for composition claims.

A REFERENCE TEACHING PRODUCT APPEARING TO BE SUBSTANTIALLY IDENTICAL IS MADE THE BASIS OF A REJECTION, AND THE EXAMINER PRESENTS EVIDENCE OR REASONING TENDING TO SHOW INHERENCY, THE BURDEN SHIFTS TO THE APPLICANT TO SHOW AN UNOBVIOUS DIFFERENCE

"[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency' under 35 U.S.C. 102, on prima facie obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted]." The burden of proof is similar to that required with respect to product-by-process claims. *In re Fitzgerald,* 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting *In re Best,* 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)).

Claims 78, 86, 88, 110, and 112 are drafted in the product-by-process format. Even though the reference may not describe the production of the molecule using the methods identical to that recited in the claims, the recitation of a process limitation in the instant claims is not viewed as positively limiting the claimed product absent a showing that the process of making recited in the instant claims imparts a novel or unexpected property to the claimed product, as it is assumed that equivalent products are obtainable by multiple routes. The burden is placed upon the applicants to establish a patentable distinction between the claimed and disclosed prior art products.

The method in which the isolated RNAs were produced is immaterial to their patentability. "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re* Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP 2113.

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Claims 110, 112, 116, 118, 119, 120, and 122 are rejected under 35 U.S.C. 102(b) as being anticipated by Roshak et al. (1996) *J. Biol. Chem.* 271:31496-31501, as evidenced by the NCBI BLAST, as available online on 10/12/2007 at http://www.ncbi.nlm.nih.gov/blast.

Roshak et al. disclose 22-nucleotide dsDNAs (see page 31497, left column). In one instance, the dsDNA comprises the sequence "agttgaggggactttcccaggc"; in another, the sequence "agttgaggcgactttcccaggc." See page 31497, left column, second paragraph.

In the materials and methods, at page 31497, it is said the double stranded DNA decoys were first synthesized by phosphoramidate chemistry as single stranded 22-mer phosphorothioate oligonucleotides, and then annealed according to standard protocols to form the double stranded duplex. Phosphoramidate chemistry would appear to preserve the 3'-OH group of the resulting oligonucleotide.

While the dsDNAs of Roshak et al. are not taught for use in RNAi, dsDNAs, are, nevertheless, disclosed in the prior art as shown by Roshak et al. The instant claims embrace dsDNAs having sequence correspondence to an mRNA to mediate RNAi. The dsDNAs of Roshak et al. have sequence correspondence to at least one mammalian mRNA, as evidenced by the alignment shown below.

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>    ref|NM_006058.3|  Homo sapiens TNFAIP3 interacting protein 1 (TNIP1), mRNA
Length=3268

 Score = 30.2 bits (15),  Expect = 7.9
 Identities = 15/15 (100%), Gaps = 0/15 (0%)
 Strand=Plus/Plus

Query  7    GGGGACTTTCCCAGG  21
            ||||||||||||||
Sbjct  360  GGGGACTTTCCCAGG  374
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Thus, the dsDNAs disclosed by Roshak et al. meet each of the structural limitations recited in the claims. Burden is shifted to Applicant to show the dsDNAs of Roshak et al. would not perform the function recited in the claims. See MPEP §2112.

For these reasons, Roshak et al. anticipate the instant claims.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis V. Wollenberger whose telephone number is 571-272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on (571)272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Louis Wollenberger/
Examiner, Art Unit 1635
October 12, 2007